

Oncology Clinical Pathways

Chronic Lymphocytic Leukemia (CLL) and Small Lymphocytic Lymphoma (SLL)

April 2024 – V2.2024



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U.S. Department
of Veterans Affairs

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CLL and SLL – Presumptive Conditions

VA automatically presumes that certain disabilities were caused by military service. This is because of the unique circumstances of a specific Veteran's military service. If a presumed condition is diagnosed in a Veteran within a certain group, they can be awarded disability compensation.

Atomic Veterans – Exposure to Ionizing Radiation

- Lymphomas, other than Hodgkin's disease

Vietnam Veterans – Agent Orange Exposure or Specified Locations

- Chronic lymphocytic leukemia (CLL)

Gulf War and Post 9/11 Veterans

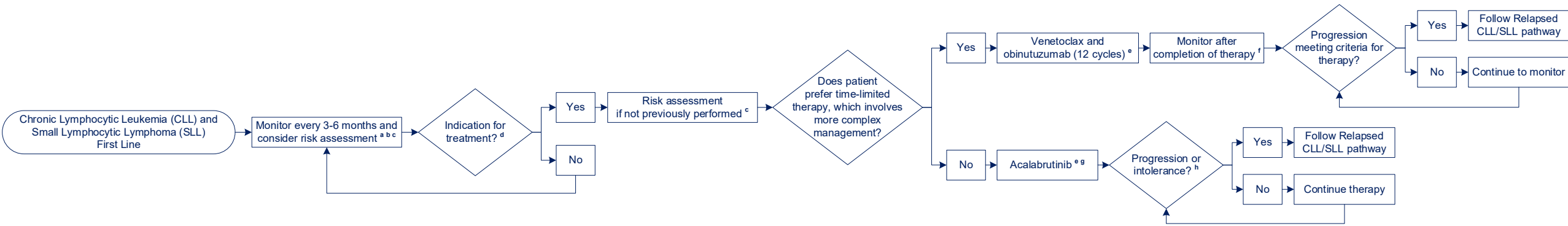
If the patient served on or after Sept. 11, 2001, in Afghanistan, Djibouti, Egypt, Jordan, Lebanon, Syria, Uzbekistan, or Yemen or if the patient served in the *Southwest Asia theater of operations, or Somalia, on or after Aug. 2, 1990, specific conditions include:

- Lymphoma of any type

* The Southwest Asia theater of operations refers to Iraq, Kuwait, Saudi Arabia, the neutral zone between Iraq and Saudi Arabia, Bahrain, Qatar, the United Arab Emirates, Oman, the Gulf of Aden, the Gulf of Oman, the Persian Gulf, the Arabian Sea, the Red Sea, and the airspace above these locations.

For more information, please visit [U.S. Department of Veterans Affairs - Presumptive Disability Benefits \(va.gov\)](https://www.va.gov/presumptive-disability-benefits)

CLL and SLL – First Line



Clinical trial(s) always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov

^a **General Supportive Care for CLL/SLL** includes IVIG for hypogammaglobulinemia and frequent infections, vaccinations (e.g. COVID, influenza, pneumococcus, and varicella-zoster virus); do not administer live attenuated vaccines; screen for secondary malignancies, particularly non-melanoma skin cancers

^b **Monitor** consider hepatitis B and C and HIV testing at baseline; monitoring frequency dependent on current symptoms, patient preference, absolute lymphocyte doubling time

^c **Risk Assessment** using CLL/SLL IPI score which includes CLL/SLL FISH panel, TP53 mutation status, serum beta-2-microglobulin, IGHV mutation status, Rai or Binet staging, and age; also consider checking FISH t(11;14) to rule out mantle cell lymphoma, and CpG-stimulated karyotype; CLL FISH panel should include probes for: 13q, 17p, 11q, and 12

^d **Indications for Treatment** include anemia (Hgb <10 g/dL) hemoglobin < 10 g/dL, platelets < 100,000/mm3, thrombocytopenia/anemia must be non-immune and not related to alternate causes, B-symptoms, and symptomatic adenopathy; consider cross-sectional imaging prior to initiation of therapy

^e **Supportive Care and Pre-Treatment Evaluation During Therapy** Includes: 1) Hepatitis B serologies if not already checked, particularly with anti-CD20 antibodies (rituximab, obinutuzumab, ofatumumab), 2) TLS risk stratification prior to Venetoclax initiation, with prevention strategies as recommended by manufacturer, 3) provide COVID prophylaxis dependent on availability, and 4) consider HSV/VZV prophylaxis

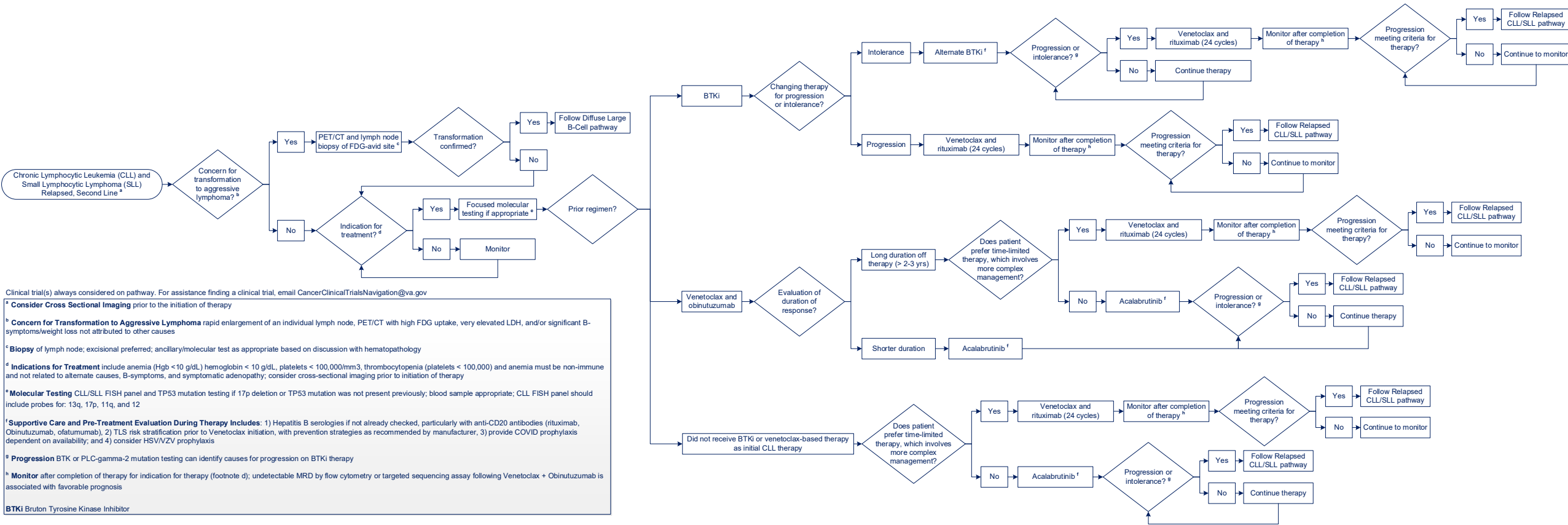
^f **Monitor** after completion of therapy for indication for therapy (footnote d); undetectable MRD by flow cytometry or targeted sequencing assay following venetoclax + obinutuzumab is associated with favorable prognosis

^g **BTK Inhibitor** avoid BTKi in severe hepatic impairment

^h **Progression** BTK or PLC-gamma-2 mutation testing can identify causes for progression on BTKi therapy but is not recommended

BTKi Bruton Tyrosine Kinase Inhibitor

CLL and SLL – Relapsed, Second Line



Clinical trial(s) always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov

^a Consider Cross Sectional Imaging prior to the initiation of therapy

^b Concern for Transformation to Aggressive Lymphoma rapid enlargement of an individual lymph node, PET/CT with high FDG uptake, very elevated LDH, and/or significant B-symptoms/weight loss not attributed to other causes

^c Biopsy of lymph node; excisional preferred; ancillary/molecular test as appropriate based on discussion with hematopathology

^d Indications for Treatment include anemia (Hgb < 10 g/dL), hemoglobin < 10 g/dL, platelets < 100,000/mm³, thrombocytopenia (platelets < 100,000) and anemia must be non-immune and not related to alternate causes, B-symptoms, and symptomatic adenopathy; consider cross-sectional imaging prior to initiation of therapy

^e Molecular Testing CLL/SLL FISH panel and TP53 mutation testing if 17p deletion or TP53 mutation was not present previously; blood sample appropriate; CLL FISH panel should include probes for: 13q, 17p, 11q, and 12

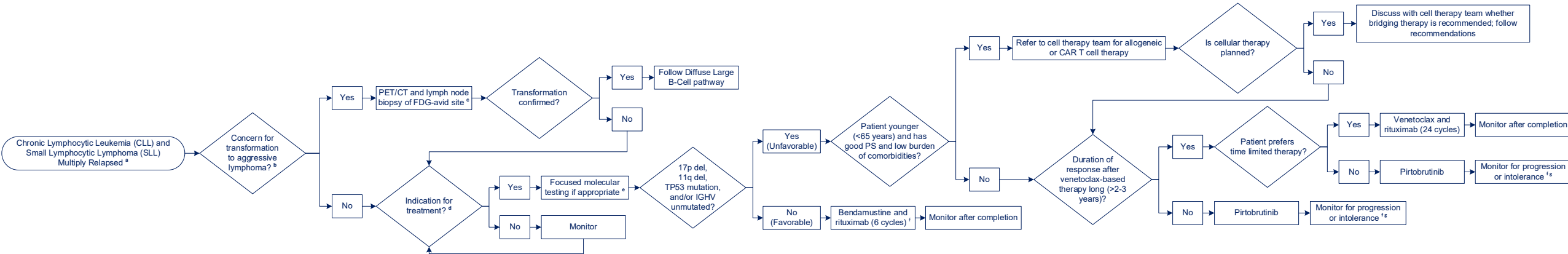
^f Supportive Care and Pre-Treatment Evaluation During Therapy Includes: 1) Hepatitis B serologies if not already checked, particularly with anti-CD20 antibodies (rituximab, Obinutuzumab, ofatumumab), 2) TLS risk stratification prior to Venetoclax initiation, with prevention strategies as recommended by manufacturer, 3) provide COVID prophylaxis dependent on availability, and 4) consider HSV/VZV prophylaxis

^g Progression BTK or PLC-gamma-2 mutation testing can identify causes for progression on BTKi therapy

^h Monitor after completion of therapy for indication for therapy (footnote d); undetectable MRD by flow cytometry or targeted sequencing assay following Venetoclax + Obinutuzumab is associated with favorable prognosis

BTKi Bruton Tyrosine Kinase Inhibitor

CLL and SLL – Multiply Relapsed



Clinical trial(s) always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov

^a **Relapsed** defined as previously treated with both BTKi and venetoclax-based therapy

^b **Concern for Transformation to Aggressive Lymphoma** rapid enlargement of an individual lymph node, PET/CT with high FDG uptake, very elevated LDH, and/or significant B- symptoms/weight loss not attributed to other causes

^c **Biopsy of Lymph Node** excisional preferred; ancillary/molecular test as appropriate based on discussion with hematopathology

^d **Indications** include anemia (Hgb <10 g/dL) hemoglobin < 10 g/dL, platelets < 100,000/mm³, thrombocytopenia (platelets < 100,000) and anemia must be non-immune and not related to alternate causes, B-symptoms, and symptomatic adenopathy; consider cross-sectional imaging prior to initiation of therapy

^e **Molecular Testing** IGHV mutation status and CLL/SLL FISH panel and TP53 mutation testing if 17p deletion or TP53 mutation was not present previously; blood sample appropriate; CLL FISH panel should include probes for: 13q, 17p, 11q, and 12

^f **Supportive Care and Pre-Treatment Evaluation During Therapy Includes:** 1) Hepatitis B serologies if not already checked, particularly with CD20 antibodies (rituximab, Obinutuzumab, ofatumumab), 2) TLS risk stratification prior to Venetoclax initiation, with prevention strategies as recommended by manufacturer, 3) provide COVID prophylaxis dependent on availability, and 4) consider HSV/VZV prophylaxis

BTKi Bruton Tyrosine Kinase Inhibitor

CLL and SLL – Molecular Testing Table

Eligibility	Test Category	Test Type	Recommended Vendors	NPOP Coverage	Specimen Type
Initial Diagnosis of Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL)	FISH	FISH panel should include probes for chromosomes 13q, 17p, 11q, and 12, t(11;14)	Local VA or locally contracted vendor	No	Bone Marrow Biopsy, Lymph Node Biopsy, Blood
	Molecular Testing	TP53 sequencing	Local VA or locally contracted vendor	No	Bone Marrow Biopsy, Lymph Node Biopsy, Blood
	Molecular Testing	IGHV hyper mutation status	Local VA or locally contracted vendor	No	Bone Marrow Biopsy, Lymph Node Biopsy, Blood
	Karyotyping	CpG-stimulated karyotype	Local VA or locally contracted vendor	No	Bone Marrow Biopsy, Lymph Node Biopsy, Blood
Relapsed Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL)	FISH	FISH panel should include probes for chromosomes 13q, 17p, 11q, and 12	Local VA or locally contracted vendor	No	Bone Marrow Biopsy, Lymph Node Biopsy, Blood
	Molecular Testing	TP53 (If alteration not detected previously)	Local VA or locally contracted vendor	No	Bone Marrow Biopsy, Lymph Node Biopsy, Blood
	Molecular Testing	BTK and PLCG2 sequencing (if BTK inhibitor resistant)	Local VA or locally contracted vendor	No	Bone Marrow Biopsy, Lymph Node Biopsy, Blood
Monitoring After Completion of Therapy	MRD Test	MRD detection by flow cytometry or NGS (if clinically indicated)	Local VA or locally contracted vendor	No	Bone Marrow Biopsy, Lymph Node Biopsy, Blood